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☐	L47	6329499.pn.	1
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☐	L46	WO-9616086-A1.did.	1
☐	L45	WO-9616086-A1.did.	1
		DB=DWPI; PLUR=YES; OP=OR	
☐	L44	9616086	4
		DB=USPT; PLUR=YES; OP=OR	
☐	L43	7265208.pn.	1
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☐	L40	WO2000001732	0
☐	L39	Wo200001732	0
☐	L38	20000113	7558
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☐	L37	5858980.pn.	2
☐	L36	5116964.pn.	3
☐	L35	L34 not @ay>"2001"	28
☐	L34	L33 and (myelin)adj(basic)adj(protein)	71
☐	L33	immunoadhesin	3829
☐	L32	L31 and MBP	9
☐	L31	L30 and (Ig)same(Fc)	45
☐	L30	L29 and fusion	1356
☐	L29	(530/326).ccls.	2937
☐	L28	L27 and MBP	25
☐	L27	L25 and (Ig)same(Fc)	317
☐	L26	L25 and (Ig)same(Fc)same(MBP)	0
☐	L25	L24 and fusion	1651
☐	L24	(530/387.3).ccls.	1924
☐	L23	L22 and MBP	5
☐	L22	L21 and Fc	41

☐	L21	L20 and (Ig)adj(fusion)	48
☐	L20	(424/134.1).ccls.	388
☐	L19	L18 and (myelin)adj(basic)adj(protein)	6
☐	L18	L17 and (Fc)adj(fusion)	104
☐	L17	(424/185.1).ccls.	2685
☐	L16	L15 and (myelin)adj(basic)adj(protein)	38
☐	L15	L14 and Fc	397
☐	L14	(424/192.1).ccls.	1018
☐	L13	(immunoadhesin)same(myelin)adj(basic)adj(protein)	9
☐	L12	(myelin)adj(basic)adj(protein)adj(fusion)same(Ig)	0
☐	L11	(saxon)adj(andrew)	13
☐	L10	L2 and (MBP)	105
☐	L9	L8 and (IgE)adj(receptor)	18
☐	L8	L2 and autoimmune	398
☐	L7	L6 and autoimmune	1
☐	L6	(MBP-Ig)	1
☐	L5	(IgG-MBP)	0
☐	L4	L2 and (Fc-MBP)	0
☐	L3	L2 and (MBP-Fc)	0
☐	L2	L1 and (myelin)adj(basic)adj(protein)	468
☐	L1	(Fc)adj(fusion)	4813

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=> s fusion protein
L1      219919 FUSION PROTEIN

=> s l1 and myelin basic  protein
L2         579 L1 AND MYELIN BASIC PROTEIN

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L3          39 L2 AND FC

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L5           9 L4 AND PD<20010501

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L5   ANSWER 1 OF 9     MEDLINE on STN
2001364658.    PubMed ID: 11418697.   A retro-inverso peptide mimic of CD28
     encompassing the MYPPPY motif adopts a polyproline type II helix and
     inhibits encephalitogenic T cells in vitro. Srinivasan M; Wardrop R M;
     Gienapp I E; Stuckman S S; Whitacre C C; Kaumaya P T. (Department of
     Microbiology, College of Biological Sciences, Ohio State University,
     Columbus, OH 43210, USA. ) Journal of immunology (Baltimore, Md. : 1950),
     (2001 Jul 1) Vol. 167, No. 1, pp. 578-85.  Journal code: 2985117R.
     ISSN: 0022-1767. Pub. country: United States. Language: English.
AB   Complete activation of T cells requires two signals: an Ag-specific signal
     delivered via the TCR by the peptide-MHC complex and a second
     costimulatory signal largely provided by B7:CD28/CTLA-4 interactions.
     Previous studies have shown that B7 blockade can either ameliorate
     experimental autoimmune encephalomyelitis by interfering with CD28
     signaling or exacerbate the disease by concomitant blockade of CTLA-4
     interaction.  Therefore, we developed a functional CD28 mimic to
     selectively block B7:CD28 interactions.  The design, synthesis, and
     structural and functional properties of the CD28 free peptide, the end
     group-blocked CD28 peptide, and its retro-inverso isomer are shown.  The
     synthetic T cell-costimulatory receptor peptides fold into a polyproline
     type II helical structure commonly seen in regions of globular proteins
     involved in transient protein-protein interactions.  The binding
     determinants of CD28 can be transferred onto a short peptide mimic of its
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ligand-binding region. The CD28 peptide mimics effectively block the expansion of encephalitogenic T cells in vitro suggesting the potential usefulness of the peptides for the treatment of autoimmune disease conditions requiring down-regulation of T cell responses.

L5 ANSWER 2 OF 9 MEDLINE on STN

2000279904. PubMed ID: 10818225. The in vitro activity of ADAM-10 is inhibited by TIMP-1 and TIMP-3. Amour A; Knight C G; Webster A; Slocombe P M; Stephens P E; Knauper V; Docherty A J; Murphy G. (School of Biological Sciences, University of East Anglia, Norwich, UK.) FEBS letters, **(2000 May 19)** Vol. 473, No. 3, pp. 275-9. Journal code: 0155157. ISSN: 0014-5793. Pub. country: Netherlands. Language: English.

AB A recombinant soluble form of the catalytic domain of human ADAM-10 was expressed as an **Fc fusion protein** from myeloma cells. The ADAM-10 was catalytically active, cleaving **myelin basic protein** and peptides based on the previously described 'metallosheddase' cleavage sites of tumour necrosis factor alpha, CD40 ligand and amyloid precursor protein. The **myelin basic protein** degradation assay was used to demonstrate that hydroxamate inhibitors of matrix metalloproteinases (MMPs) were also inhibitors of ADAM-10. The natural MMP inhibitors, TIMP-2 and TIMP-4 were unable to inhibit ADAM-10, but TIMP-1 and TIMP-3 were inhibitory. Using a quenched fluorescent substrate assay and ADAM-10 we obtained approximate apparent inhibition constants of 0.1 nM (TIMP-1) and 0.9 nM (TIMP-3). The TIMP-1 inhibition of ADAM-10 could therefore prove useful in distinguishing its activity from that of TACE, which is only inhibited by TIMP-3, in cell based assays.

L5 ANSWER 3 OF 9 MEDLINE on STN

1998230504. PubMed ID: 9570577. Expansion of autoreactive T cells in multiple sclerosis is independent of exogenous B7 costimulation. Scholz C; Patton K T; Anderson D E; Freeman G J; Hafler D A. (Laboratory of Molecular Immunology, Department of Neurology, Brigham and Women's Hospital, Boston, MA 02115, USA.) Journal of immunology (Baltimore, Md. : 1950), **(1998 Feb 1)** Vol. 160, No. 3, pp. 1532-8. Journal code: 2985117R. ISSN: 0022-1767. Pub. country: United States. Language: English.

AB Multiple sclerosis (MS) is an inflammatory disease of the myelinated central nervous system that is postulated to be induced by myelin-reactive CD4 T cells. T cell activation requires an antigen-specific signal through the TCR and a costimulatory signal, which can be mediated by B7-1 or B7-2 engagement of CD28. To directly examine the activation state of myelin-reactive T cells in MS, the costimulation requirements necessary to activate **myelin basic protein** (MBP) or tetanus toxoid (TT)-reactive CD4 T cells were compared between normal controls and MS patients. Peripheral blood T cells were stimulated with Chinese hamster ovary (CHO) cells transfected either with DRB1*1501/DRA0101 chains (t-DR2) alone, or in combination with, B7-1 or B7-2. In the absence of costimulation, T cells from normal subjects stimulated with the recall antigen TT p830-843 were induced to expand and proliferate, but stimulation with MBP p85-99 did not have this effect. In marked contrast, T cells from patients with MS stimulated with MBP p85-99 in the absence of B7-1 or B7-2 signals expanded and proliferated. Thus, MBP-reactive CD4 T cells in patients with MS are costimulation independent and have been previously activated in vivo. These experiments provide further direct evidence for a role of activated MBP-specific CD4 T cells in the pathogenesis of MS.

L5 ANSWER 4 OF 9 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN

2000:323738 Document No.: PREV200000323738. Kinetics of T-cell receptor binding by bivalent HLA-DRcntdotpeptide complexes that activate antigen-specific human T-cells. Appel, Heiner; Gauthier, Laurent; Pyrdol, Jason; Wucherpfennig, Kai W. [Reprint author]. Dept. of Cancer Immunology and AIDS, Dana-Farber Cancer Institute, Boston, MA, 02115, USA. Journal of Biological Chemistry, (**January 7, 2000**) Vol. 275, No. 1, pp. 312-321. print.

CODEN: JBCHA3. ISSN: 0021-9258. Language: English.

AB Monovalent major histocompatibility complex-peptide complexes dissociate within seconds from the T-cell receptor (TCR), indicating that dimerization/multimerization may be important during early stages of T-cell activation. Soluble bivalent HLA-DR2cntdotmyelin basic protein (MBP) peptide complexes were expressed by replacing the F(ab) arms of an IgG2a antibody with HLA-DR2cntdotMBP peptide complexes. The binding of bivalent HLA-DR2cntdotpeptide complexes to recombinant TCR was examined by surface plasmon resonance. The bivalent nature greatly enhanced TCR binding and slowed dissociation from the TCR, with a t1/2 of 2.1 to 4.6 min. Soluble bivalent HLA-DR2cntdotMBP peptide complexes activated antigen-specific T-cells in the absence of antigen presenting cells. In contrast, soluble antibodies to the TCRcntdotCD3 complex were ineffective, indicating that they failed to induce an active TCR dimer. TCR/CD3 antibodies induced T-cell proliferation when bound by antigen presenting cells that expressed **Fc** receptors. In the presence of dendritic cells, bivalent HLA-DR2cntdotMBP peptide complexes induced T-cell activation at >100-fold lower concentrations than TCR/CD3 antibodies and were also superior to peptide or antigen. These results demonstrate that bivalent HLA-DRcntdotpeptide complexes represent effective ligands for activation of the TCR. The data support a role for TCR dimerization in early TCR signaling and kinetic proofreading.

L5 ANSWER 5 OF 9 SCISEARCH COPYRIGHT (c) 2007 The Thomson Corporation on STN

1995:380552 The Genuine Article (R) Number: RB212. LONG-TERM INHIBITION OF MURINE EXPERIMENTAL AUTOIMMUNE ENCEPHALOMYELITIS USING CTLA-4-**FC** SUPPORTS A KEY ROLE FOR CD28 COSTIMULATION. CROSS A H (Reprint); GIRARD T J; GIACOLETTO K S; EVANS R J; KEELING R M; LIN R F; TROTTER J L; KARR R W. WASHINGTON UNIV, SCH MED, DEPT NEUROL & NEUROSURG, ST LOUIS, MO 63110; GD SEARLE & CO, DEPT IMMUNOL, ST LOUIS, MO 63198. JOURNAL OF CLINICAL INVESTIGATION (**JUN 1995**) Vol. 95, No. 6, pp. 2783-2789. ISSN: 0021-9738. Publisher: ROCKEFELLER UNIV PRESS, 222 E 70TH STREET, NEW YORK, NY 10021. Language: English.

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB T cell activation involves not only recognition of antigen presented by the MHC, but also nonspecific interactions termed ''costimulation.'' The costimulatory molecules B7-1 and B7-2 are ligands on antigen-presenting cells for the CD28 and CTLA-4 receptors on T cells. Previously, a **fusion protein** consisting of human CTLA-4 linked to human **Fc** was shown to bind B7-1 and B7-2 with high avidity and to prevent specific T cell activation. Here we investigated the effects of a recombinant **fusion protein** consisting of the extracellular domain of human CTLA-4 bound to mouse IgG2a **Fc** (CTLA-4-**Fc**) upon experimental autoimmune encephalomyelitis, a T cell-mediated disease that serves as a model for multiple sclerosis. CTLA-4-**Fc** prevented experimental autoimmune encephalomyelitis in 26 of 28 CTLA-4-**Fc**-treated mice (median maximum score 0), whereas 28 of 30 mice treated with control mouse IgG2a developed disease (median maximum score 2.75). Less inflammation and virtually no demyelination or axonal loss occurred in CTLA-4-**Fc** -treated compared with control-treated mice, Activated splenocytes from CTLA-4-**Fc**-treated mice were able to transfer disease adoptively to naive recipients. These results indicate a key role for the B7/CD28 system in the development of actively induced murine experimental autoimmune encephalomyelitis, suggesting an area of investigation with therapeutic potential for multiple sclerosis.

L5 ANSWER 6 OF 9 CAPLUS COPYRIGHT 2007 ACS on STN

2000:186966 Document No. 133:176116 A gene therapy or purified CTLA4IgG treatment of experimental allergic encephalomyelitis. Kawaguchi, Yoshinori (Section of Immunopathogenesis, Institute of Immunological Science, Hokkaido University, Sapporo, 060-0815, Japan). Hokkaido Igaku Zasshi, 74(6), 467-475 (English) **1999.** CODEN: HOIZAK. ISSN: 0367-6102. Publisher: Hokkaido Igakkai.

AB We examined whether multiple i.p. injection of a soluble form of a chimeric protein consisting of an extracellular portion of cytotoxic T lymphocyte-associated protein 4 and an **Fc** portion of human IgG1(CTLA4IgG) at the initiation phase could successfully control the subsequent development of exptl. allergic encephalomyelitis (EAE). We demonstrated that CTLA4IgG treatment could delay the onset and reduce the severity of EAE in early phase of disease development. More importantly, CTLA4IgG treatment significantly reduced the incidence of EAE. This was in good agreement to that spleen cells obtained from CTLA4IgG-treated animals responded poorly to **myelin basic protein** (MBP) in vitro as compared to those from human IgG-treated animals. However, the CTLA4IgG-treated mice eventually developed EAE and after all, incidence of EAE was not significantly different from that in control group. We then tested whether a gene therapy using adenovirus vector containing CTLA4IgG (Adex1CACTLA4IgG) could inhibit the development of EAE. We demonstrated that incidence and severity of EAE were significantly inhibited by a single injection of i.v. Adex1CACTLA4IgG up to 8 mo. Thus, this study demonstrated the efficacy of a single dose of adenovirus-mediated gene therapy in controlling EAE as compared to repeated injection of purified CTLA4IgG proteins.

L5 ANSWER 7 OF 9 CAPLUS COPYRIGHT 2007 ACS on STN

2000:34907 Document No. 132:92309 Compounds, compositions and methods for the endocytic presentation of immunosuppressive factors. Zaghouani, Habib (The University of Tennessee Research Corporation, USA). PCT Int. Appl. WO 2000001732 A2 **20000113**, 80 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, CZ, DE, DE, DK, DK, EE, EE, ES, FI, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1999-US15225 19990706. PRIORITY: US 1998-111123 19980706.

AB A **fusion protein** for the alleviation of symptoms associated with an autoimmune disorder comprising an Ig or portion thereof linked to one or more autoantigenic polypeptides or fragments thereof, wherein said Ig or portion thereof is capable of binding to an **Fc** receptor and being endocytosed by an antigen-presenting cell, and said one or more autoantigenic polypeptides or fragments thereof provides more than one T cell receptor peptide agonist for presentation on the surface of said antigen-presenting cell upon endocytic processing. Said autoantigenic polypeptides may comprise at least a portion of **myelin basic protein** or at least a portion of proteolipid protein. Method to alleviate symptoms associated with an autoimmune disorder in a patient in need thereof comprising the steps of providing a composition comprising said **fusion protein** and administering a therapeutically effective amount of said composition to said patient. Autoimmune disorders may include multiple sclerosis, lupus, rheumatoid arthritis, scleroderma, insulin-dependent diabetes and ulcerative colitis. Method for presenting multiple T cell receptor agonists on the surface of a professional or nonprofessional antigen-presenting cell comprising the steps of providing said **fusion protein**, contacting said **fusion protein** with at least one **Fc** receptor present on the surface of a professional or nonprofessional antigen-presenting cell, whereby the **fusion protein** is internalized by the antigen-presenting cell, and endocytically processing the internalized **fusion protein** to provide more than one T cell receptor peptide agonist, wherein the provided T cell receptor agonists are presented on the surface of the antigen-presenting cell.

L5 ANSWER 8 OF 9 CAPLUS COPYRIGHT 2007 ACS on STN

1999:549393 Document No. 131:183867 Monovalent, multivalent, and multimeric

MHC binding domain **fusion proteins** and conjugates, and uses therefor. Wucherpfennig, Kai W.; Strominger, Jack L. (President and Fellows of Harvard College, USA). PCT Int. Appl. WO 9942597 A1 **19990826**, 113 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1999-US3603 19990219. PRIORITY: US 1998-PV75351 19980219.

AB The present invention is directed to the design, production, and use of monovalent, multivalent and multimeric major histocompatibility complex binding domain **fusion proteins** and conjugates. The MHC **fusion proteins** and conjugates may comprise MHC class II α or β chain (HLA-DRA*0101, HLA-DRA*0102, HLA-DQA1*0301, HLA-DRB1*01, etc.), leucine zipper domain of Fos or Jun, linker peptide, yeast σ-mating factor secretion signal, human **myelin basic protein** tag, IgG or IgE or IgM **Fc**, and optionally cytotoxic substance (human desmoglein 3 protein peptide). The MHC binding domain **fusion proteins** and conjugates are useful for diagnosis and treatment of diseases associated with T cell-mediated immune response and antigen presentation, e.g. autoimmune disease, multiple sclerosis and rheumatoid arthritis. Thus, **fusion proteins** containing HLA-DR2 α chain (β chain), Fos (Jun) leucine zipper dimerization domain, VDGGGGG linker, and α-mating secretion signal were prepared, fused with IgG2a or IgM, tagged with MBP peptide, conjugated with bead carrier, and used for selectively depletion of T cells.

L5 ANSWER 9 OF 9 CAPLUS COPYRIGHT 2007 ACS on STN

1996:352596 Document No. 125:31803 Inhibition by CTLA4Ig of experimental allergic encephalomyelitis. Arima, Takeshi; Rehman, Atiq; Hickey, William F.; Flye, M. Wayne (Dep. Surg., Washington Univ. Sch. Med., St. Louis, MO, 63110, USA). Journal of Immunology, 156(12), 4916-4924 (English) **1996.** CODEN: JOIMA3. ISSN: 0022-1767. Publisher: American Association of Immunologists.

AB B7-1 and B7-2 are well characterized costimulatory ligands on Ag presentation cells for the CD28 and CTLA4 receptors on T cells. The **fusion protein** CTLA4Ig can block this interaction and prevent specific T cell activation. The development of fatal CD4+ T cell-mediated exptl. allergic encephalomyelitis (EAE) in susceptible female Lewis rats was optimized by immunization with 20 mg of guinea pig spinal cord homogenate in CFA on day 0 with three doses of 1 μg pertussis toxin given i.v. on days 0, 3, and 7. This immunization regimen uniformly resulted in the development of severe clin. neurol. signs of EAE with 100% mortality by day 17 postimmunization. Treatment with 0.5 mg/dose of rhCTLA4-Ig on days -2, 0, 3, 6, 9, 12, 15, and 18 significantly decreased the incidence, delayed the onset, and reduced the severity of clin. EAE ($p = 0.0002$ vs control by the Mann-Whitney U test) enough to completely prevent fatal EAE, whereas treatment with control human IgG had no effect. Histol., perivascular neutrophilic infiltrates were also dramatically decreased in the spinal cords of animals treated with CTLA4 but not in those treated with control human IgG. The proliferative response to encephalitogenic Ags (guinea pig **myelin basic protein** and proteolipid protein) by lymph node cells from animals immunized with guinea pig spinal cord 10 days before was also significantly suppressed in vitro by CTLA4Ig (1 μg/mL). However, the protective effect of CTLA4Ig could be completely prevented by the daily i.p. administration, from day 0 to 10, of exogenous human rIL-2 (180,000 IU). These results indicate a critical requirement of the costimulatory B7/CD28 pathway early in the development of CD4+ T cell-mediated EAE in the rat.

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=> s myelin basic protein
L6        38982 MYELIN BASIC PROTEIN

=> s l6 and fusion
L7          858 L6 AND FUSION

=> s l7 and Fc
L8           44 L7 AND FC

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L11  ANSWER 1 OF 10      MEDLINE on STN
2001364658.    PubMed ID: 11418697.   A retro-inverso peptide mimic of CD28
     encompassing the MYPPPY motif adopts a polyproline type II helix and
     inhibits encephalitogenic T cells in vitro. Srinivasan M; Wardrop R M;
     Gienapp I E; Stuckman S S; Whitacre C C; Kaumaya P T. (Department of
     Microbiology, College of Biological Sciences, Ohio State University,
     Columbus, OH 43210, USA. ) Journal of immunology (Baltimore, Md. : 1950),
     (2001 Jul 1) Vol. 167, No. 1, pp. 578-85.  Journal code: 2985117R.
     ISSN: 0022-1767. Pub. country: United States. Language: English.
AB   Complete activation of T cells requires two signals: an Ag-specific signal
     delivered via the TCR by the peptide-MHC complex and a second
     costimulatory signal largely provided by B7:CD28/CTLA-4 interactions.
     Previous studies have shown that B7 blockade can either ameliorate
     experimental autoimmune encephalomyelitis by interfering with CD28
     signaling or exacerbate the disease by concomitant blockade of CTLA-4
     interaction.  Therefore, we developed a functional CD28 mimic to
     selectively block B7:CD28 interactions.  The design, synthesis, and
     structural and functional properties of the CD28 free peptide, the end
     group-blocked CD28 peptide, and its retro-inverso isomer are shown.  The
     synthetic T cell-costimulatory receptor peptides fold into a polyproline
     type II helical structure commonly seen in regions of globular proteins
     involved in transient protein-protein interactions.  The binding
     determinants of CD28 can be transferred onto a short peptide mimic of its
     ligand-binding region.  The CD28 peptide mimics effectively block the
     expansion of encephalitogenic T cells in vitro suggesting the potential
     usefulness of the peptides for the treatment of autoimmune disease
     conditions requiring down-regulation of T cell responses.

L11  ANSWER 2 OF 10  CAPLUS  COPYRIGHT 2007 ACS on STN
2000:34907   Document No. 132:92309  Compounds, compositions and methods for
     the endocytic presentation of immunosuppressive factors.  Zaghouani, Habib
     (The University of Tennessee Research Corporation, USA).  PCT Int. Appl.
     WO 2000001732 A2 20000113, 80 pp.  DESIGNATED STATES: W:  AE,
     AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, CZ, DE, DE,
     DK, DK, EE, EE, ES, FI, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS,
     JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW,
     MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK, SL, TJ, TM, TR, TT,
     UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW:
     AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR,
     IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG.  (English).  CODEN:
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PIXXD2. APPLICATION: WO 1999-US15225 19990706. PRIORITY: US 1998-111123 19980706.

AB A **fusion** protein for the alleviation of symptoms associated with an autoimmune disorder comprising an Ig or portion thereof linked to one or more autoantigenic polypeptides or fragments thereof, wherein said Ig or portion thereof is capable of binding to an **Fc** receptor and being endocytosed by an antigen-presenting cell, and said one or more autoantigenic polypeptides or fragments thereof provides more than one T cell receptor peptide agonist for presentation on the surface of said antigen-presenting cell upon endocytic processing. Said autoantigenic polypeptides may comprise at least a portion of **myelin basic protein** or at least a portion of proteolipid protein. Method to alleviate symptoms associated with an autoimmune disorder in a patient in need thereof comprising the steps of providing a composition comprising said **fusion** protein and administering a therapeutically effective amount of said composition to said patient. Autoimmune disorders may include multiple sclerosis, lupus, rheumatoid arthritis, scleroderma, insulin-dependent diabetes and ulcerative colitis. Method for presenting multiple T cell receptor agonists on the surface of a professional or nonprofessional antigen-presenting cell comprising the steps of providing said **fusion** protein, contacting said **fusion** protein with at least one **Fc** receptor present on the surface of a professional or nonprofessional antigen-presenting cell, whereby the **fusion** protein is internalized by the antigen-presenting cell, and endocytically processing the internalized **fusion** protein to provide more than one T cell receptor peptide agonist, wherein the provided T cell receptor agonists are presented on the surface of the antigen-presenting cell.

L11 ANSWER 3 OF 10 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN

2000:323738 Document No.: PREV200000323738. Kinetics of T-cell receptor binding by bivalent HLA-DRcntdotpeptide complexes that activate antigen-specific human T-cells. Appel, Heiner; Gauthier, Laurent; Pyrdol, Jason; Wucherpfennig, Kai W. [Reprint author]. Dept. of Cancer Immunology and AIDS, Dana-Farber Cancer Institute, Boston, MA, 02115, USA. Journal of Biological Chemistry, (**January 7, 2000**) Vol. 275, No. 1, pp. 312-321. print.
CODEN: JBCHA3. ISSN: 0021-9258. Language: English.

AB Monovalent major histocompatibility complex-peptide complexes dissociate within seconds from the T-cell receptor (TCR), indicating that dimerization/multimerization may be important during early stages of T-cell activation. Soluble bivalent HLA-DR2cntdotmyelin basic protein (MBP) peptide complexes were expressed by replacing the F(ab) arms of an IgG2a antibody with HLA-DR2cntdotMBP peptide complexes. The binding of bivalent HLA-DR2cntdotpeptide complexes to recombinant TCR was examined by surface plasmon resonance. The bivalent nature greatly enhanced TCR binding and slowed dissociation from the TCR, with a t1/2 of 2.1 to 4.6 min. Soluble bivalent HLA-DR2cntdotMBP peptide complexes activated antigen-specific T-cells in the absence of antigen presenting cells. In contrast, soluble antibodies to the TCRcntdotCD3 complex were ineffective, indicating that they failed to induce an active TCR dimer. TCR/CD3 antibodies induced T-cell proliferation when bound by antigen presenting cells that expressed **Fc** receptors. In the presence of dendritic cells, bivalent HLA-DR2cntdotMBP peptide complexes induced T-cell activation at >100-fold lower concentrations than TCR/CD3 antibodies and were also superior to peptide or antigen. These results demonstrate that bivalent HLA-DRcntdotpeptide complexes represent effective ligands for activation of the TCR. The data support a role for TCR dimerization in early TCR signaling and kinetic proofreading.

L11 ANSWER 4 OF 10 MEDLINE on STN

2000279904. PubMed ID: 10818225. The in vitro activity of ADAM-10 is inhibited by TIMP-1 and TIMP-3. Amour A; Knight C G; Webster A; Slocombe P M; Stephens P E; Knauper V; Docherty A J; Murphy G. (School of Biological

Sciences, University of East Anglia, Norwich, UK.) FEBS letters, **(2000 May 19)** Vol. 473, No. 3, pp. 275-9. Journal code: 0155157. ISSN: 0014-5793. Pub. country: Netherlands. Language: English.

AB A recombinant soluble form of the catalytic domain of human ADAM-10 was expressed as an **Fc fusion** protein from myeloma cells. The ADAM-10 was catalytically active, cleaving **myelin basic protein** and peptides based on the previously described 'metallosheddase' cleavage sites of tumour necrosis factor alpha, CD40 ligand and amyloid precursor protein. The **myelin basic protein** degradation assay was used to demonstrate that hydroxamate inhibitors of matrix metalloproteinases (MMPs) were also inhibitors of ADAM-10. The natural MMP inhibitors, TIMP-2 and TIMP-4 were unable to inhibit ADAM-10, but TIMP-1 and TIMP-3 were inhibitory. Using a quenched fluorescent substrate assay and ADAM-10 we obtained approximate apparent inhibition constants of 0.1 nM (TIMP-1) and 0.9 nM (TIMP-3). The TIMP-1 inhibition of ADAM-10 could therefore prove useful in distinguishing its activity from that of TACE, which is only inhibited by TIMP-3, in cell based assays.

L11 ANSWER 5 OF 10 CAPLUS COPYRIGHT 2007 ACS on STN

1999:549393 Document No. 131:183867 Monovalent, multivalent, and multimeric MHC binding domain **fusion** proteins and conjugates, and uses therefor. Wucherpfennig, Kai W.; Strominger, Jack L. (President and Fellows of Harvard College, USA). PCT Int. Appl. WO 9942597 A1 **19990826**, 113 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1999-US3603 19990219. PRIORITY: US 1998-PV75351 19980219.

AB The present invention is directed to the design, production, and use of monovalent, multivalent and multimeric major histocompatibility complex binding domain **fusion** proteins and conjugates. The MHC **fusion** proteins and conjugates may comprise MHC class II α or β chain (HLA-DRA*0101, HLA-DRA*0102, HLA-DQA1*0301, HLA-DRB1*01, etc.), leucine zipper domain of Fos or Jun, linker peptide, yeast σ-mating factor secretion signal, human **myelin basic protein** tag, IgG or IgE or IgM **Fc**, and optionally cytotoxic substance (human desmoglein 3 protein peptide). The MHC binding domain **fusion** proteins and conjugates are useful for diagnosis and treatment of diseases associated with T cell-mediated immune response and antigen presentation, e.g. autoimmune disease, multiple sclerosis and rheumatoid arthritis. Thus, **fusion** proteins containing HLA-DR2 α chain (β chain), Fos (Jun) leucine zipper dimerization domain, VDGGGGG linker, and α-mating secretion signal were prepared, fused with IgG2a or IgM, tagged with MBP peptide, conjugated with bead carrier, and used for selectively depletion of T cells.

L11 ANSWER 6 OF 10 CAPLUS COPYRIGHT 2007 ACS on STN

2000:186966 Document No. 133:176116 A gene therapy or purified CTLA4IgG treatment of experimental allergic encephalomyelitis. Kawaguchi, Yoshinori (Section of Immunopathogenesis, Institute of Immunological Science, Hokkaido University, Sapporo, 060-0815, Japan). Hokkaido Igaku Zasshi, 74(6), 467-475 (English) **1999.** CODEN: HOIZAK. ISSN: 0367-6102. Publisher: Hokkaido Igakkai.

AB We examined whether multiple i.p. injection of a soluble form of a chimeric protein consisting of an extracellular portion of cytotoxic T lymphocyte-associated protein 4 and an **Fc** portion of human IgG1(CTLA4IgG) at the initiation phase could successfully control the subsequent development of exptl. allergic encephalomyelitis (EAE). We demonstrated that CTLA4IgG treatment could delay the onset and reduce the severity of EAE in early phase of disease development. More importantly,

CTLA4IgG treatment significantly reduced the incidence of EAE. This was in good agreement to that spleen cells obtained from CTLA4IgG-treated animals responded poorly to **myelin basic protein** (MBP) in vitro as compared to those from human IgG-treated animals. However, the CTLA4IgG-treated mice eventually developed EAE and after all, incidence of EAE was not significantly different from that in control group. We then tested whether a gene therapy using adenovirus vector containing CTLA4IgG (Adex1CACTLA4IgG) could inhibit the development of EAE. We demonstrated that incidence and severity of EAE were significantly inhibited by a single injection of i.v. Adex1CACTLA4IgG up to 8 mo. Thus, this study demonstrated the efficacy of a single dose of adenovirus-mediated gene therapy in controlling EAE as compared to repeated injection of purified CTLA4IgG proteins.

L11 ANSWER 7 OF 10 CAPLUS COPYRIGHT 2007 ACS on STN
1998:285095 Document No. 129:66611 Vaccination with DNA encoding an immunodominant **myelin basic protein** peptide targeted to **Fc** of immunoglobulin G suppresses experimental autoimmune encephalomyelitis. Lobell, Anna; Weissert, Robert; Storch, Maria K.; Svanholm, Cecilia; De Graaf, Katrien L.; Lassmann, Hans; Andersson, Roland; Olsson, Tomas; Wigzell, Hans (Microbiology and Tumorbiology Center, Karolinska Institute, Stockholm, S-171 77, Swed.). Journal of Experimental Medicine, 187(9), 1543-1548 (English) **1998**. CODEN: JEMEAV. ISSN: 0022-1007. Publisher: Rockefeller University Press.

AB The authors explore here if vaccination with DNA encoding an autoantigenic peptide can suppress autoimmune disease. For this purpose the authors used exptl. autoimmune encephalomyelitis (EAE), which is an autoaggressive disease in the central nervous system and an animal model for multiple sclerosis. Lewis rats were vaccinated with DNA encoding an encephalitogenic T cell epitope, guinea pig **myelin basic protein** peptide 68-85 (MBP68-85), before induction of EAE with MBP68-85 in complete Freund's adjuvant. Compared to vaccination with a control DNA construct, the vaccination suppressed clin. and histopathol. signs of EAE, and reduced the interferon γ production after challenge with MBP68-85. Targeting of the gene product to **Fc** of IgG was essential for this effect. There were no signs of a Th2 cytokine bias. The data suggest that DNA vaccines encoding autoantigenic peptides may be useful tools in controlling autoimmune disease.

L11 ANSWER 8 OF 10 MEDLINE on STN
1998230504. PubMed ID: 9570577. Expansion of autoreactive T cells in multiple sclerosis is independent of exogenous B7 costimulation. Scholz C; Patton K T; Anderson D E; Freeman G J; Hafler D A. (Laboratory of Molecular Immunology, Department of Neurology, Brigham and Women's Hospital, Boston, MA 02115, USA.) Journal of immunology (Baltimore, Md. : 1950), **(1998 Feb 1)** Vol. 160, No. 3, pp. 1532-8. Journal code: 2985117R. ISSN: 0022-1767. Pub. country: United States. Language: English.

AB Multiple sclerosis (MS) is an inflammatory disease of the myelinated central nervous system that is postulated to be induced by myelin-reactive CD4 T cells. T cell activation requires an antigen-specific signal through the TCR and a costimulatory signal, which can be mediated by B7-1 or B7-2 engagement of CD28. To directly examine the activation state of myelin-reactive T cells in MS, the costimulation requirements necessary to activate **myelin basic protein** (MBP) or tetanus toxoid (TT)-reactive CD4 T cells were compared between normal controls and MS patients. Peripheral blood T cells were stimulated with Chinese hamster ovary (CHO) cells transfected either with DRB1*1501/DRA0101 chains (t-DR2) alone, or in combination with, B7-1 or B7-2. In the absence of costimulation, T cells from normal subjects stimulated with the recall antigen TT p830-843 were induced to expand and proliferate, but stimulation with MBP p85-99 did not have this effect. In marked contrast, T cells from patients with MS stimulated with MBP p85-99 in the absence of B7-1 or B7-2 signals expanded and proliferated. Thus, MBP-reactive CD4 T cells in patients with MS are costimulation independent

and have been previously activated in vivo. These experiments provide further direct evidence for a role of activated MBP-specific CD4 T cells in the pathogenesis of MS.

L11 ANSWER 9 OF 10 CAPLUS COPYRIGHT 2007 ACS on STN
1996:352596 Document No. 125:31803 Inhibition by CTLA4Ig of experimental allergic encephalomyelitis. Arima, Takeshi; Rehman, Atiq; Hickey, William F.; Flye, M. Wayne (Dep. Surg., Washington Univ. Sch. Med., St. Louis, MO, 63110, USA). Journal of Immunology, 156(12), 4916-4924 (English) **1996.** CODEN: JOIMA3. ISSN: 0022-1767. Publisher: American Association of Immunologists.

AB B7-1 and B7-2 are well characterized costimulatory ligands on Ag presentation cells for the CD28 and CTLA4 receptors on T cells. The **fusion** protein CTLA4Ig can block this interaction and prevent specific T cell activation. The development of fatal CD4+ T cell-mediated exptl. allergic encephalomyelitis (EAE) in susceptible female Lewis rats was optimized by immunization with 20 mg of guinea pig spinal cord homogenate in CFA on day 0 with three doses of 1 μg pertussis toxin given i.v. on days 0, 3, and 7. This immunization regimen uniformly resulted in the development of severe clin. neurol. signs of EAE with 100% mortality by day 17 postimmunization. Treatment with 0.5 mg/dose of rhCTLA4-Ig on days -2, 0, 3, 6, 9, 12, 15, and 18 significantly decreased the incidence, delayed the onset, and reduced the severity of clin. EAE ($p = 0.0002$ vs control by the Mann-Whitney U test) enough to completely prevent fatal EAE, whereas treatment with control human IgG had no effect. Histol., perivascular neutrophilic infiltrates were also dramatically decreased in the spinal cords of animals treated with CTLA4 but not in those treated with control human IgG. The proliferative response to encephalitogenic Ags (guinea pig **myelin basic protein** and proteolipid protein) by lymph node cells from animals immunized with guinea pig spinal cord 10 days before was also significantly suppressed in vitro by CTLA4Ig (1 μg/mL). However, the protective effect of CTLA4Ig could be completely prevented by the daily i.p. administration, from day 0 to 10, of exogenous human rIL-2 (180,000 IU). These results indicate a critical requirement of the costimulatory B7/CD28 pathway early in the development of CD4+ T cell-mediated EAE in the rat.

L11 ANSWER 10 OF 10 SCISEARCH COPYRIGHT (c) 2007 The Thomson Corporation on STN
1995:380552 The Genuine Article (R) Number: RB212. LONG-TERM INHIBITION OF MURINE EXPERIMENTAL AUTOIMMUNE ENCEPHALOMYELITIS USING CTLA-4-**FC** SUPPORTS A KEY ROLE FOR CD28 COSTIMULATION. CROSS A H (Reprint); GIRARD T J; GIACOLETTO K S; EVANS R J; KEELING R M; LIN R F; TROTTER J L; KARR R W. WASHINGTON UNIV, SCH MED, DEPT NEUROL & NEUROSURG, ST LOUIS, MO 63110; GD SEARLE & CO, DEPT IMMUNOL, ST LOUIS, MO 63198. JOURNAL OF CLINICAL INVESTIGATION (**JUN 1995**) Vol. 95, No. 6, pp. 2783-2789. ISSN: 0021-9738. Publisher: ROCKEFELLER UNIV PRESS, 222 E 70TH STREET, NEW YORK, NY 10021. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB T cell activation involves not only recognition of antigen presented by the MHC, but also nonspecific interactions termed ''costimulation.'' The costimulatory molecules B7-1 and B7-2 are ligands on antigen-presenting cells for the CD28 and CTLA-4 receptors on T cells. Previously, a **fusion** protein consisting of human CTLA-4 linked to human **Fc** was shown to bind B7-1 and B7-2 with high avidity and to prevent specific T cell activation. Here we investigated the effects of a recombinant **fusion** protein consisting of the extracellular domain of human CTLA-4 bound to mouse IgG2a **Fc** (CTLA-4-**Fc**) upon experimental autoimmune encephalomyelitis, a T cell-mediated disease that serves as a model for multiple sclerosis. CTLA-4-**Fc** prevented experimental autoimmune encephalomyelitis in 26 of 28 CTLA-4-**Fc**-treated mice (median maximum score 0), whereas 28 of 30 mice treated with control mouse IgG2a developed disease (median maximum score 2.75). Less inflammation and virtually no

demyelination or axonal loss occurred in CTLA-4-**Fc**-treated compared with control-treated mice, Activated splenocytes from CTLA-4-**Fc**-treated mice were able to transfer disease adoptively to naive recipients. These results indicate a key role for the B7/CD28 system in the development of actively induced murine experimental autoimmune encephalomyelitis, suggesting an area of investigation with therapeutic potential for multiple sclerosis.

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=> s myelin basic protein chimera
L12           4 MYELIN BASIC PROTEIN CHIMERA

=> dup remove l12
PROCESSING COMPLETED FOR L12
L13           1 DUP REMOVE L12 (3 DUPLICATES REMOVED)

=> d l13 cbib abs

L13  ANSWER 1 OF 1     MEDLINE on STN                    DUPLICATE 1
2001544732.    PubMed ID: 11591739.  Neonatal exposure to antigen primes the
     immune system to develop responses in various lymphoid organs and promotes
     bystander regulation of diverse T cell specificities. Pack C D; Cestra A
     E; Min B; Legge K L; Li L; Caprio-Young J C; Bell J J; Gregg R K;
     Zaghouani H. (Department of Microbiology, University of Tennessee,
     Knoxville, TN 37996, USA. ) Journal of immunology (Baltimore, Md. : 1950),
     (2001 Oct 15) Vol. 167, No. 8, pp. 4187-95.  Journal code: 2985117R. ISSN:
     0022-1767. Pub. country: United States. Language: English.
AB   Neonatal exposure to Ag has always been considered suppressive for
     immunity.  Recent investigations, however, indicated that the neonatal
     immune system could be guided to develop immunity.  For instance, delivery
     of a proteolipid protein (PLP) peptide on Ig boosts the neonatal immune
     system to develop responses upon challenge with the PLP peptide later.
     Accordingly, mice given Ig-PLP at birth and challenged with the PLP
     peptide as adults developed proliferative T cells in the lymph node that
     produced IL-4 instead of the usual Th1 cytokines.  However, the spleen was
     unresponsive unless IL-12 was provided.  Herein; we wished to determine
     whether such a neonatal response is intrinsic to the PLP peptide or could
     develop with an unrelated myelin peptide as well as whether the T cell
     deviation is able to confer resistance to autoimmunity involving diverse T
     cell specificities.  Accordingly, the amino acid sequence 87-99 of myelin
     basic protein was expressed on the same Ig backbone, and the resulting Ig-
     myelin basic protein chimera was
     tested for induction of neonatal immunity and protection against
     experimental allergic encephalomyelitis.  Surprisingly, the results
     indicated that immunity developed in the lymph node and spleen, with
     deviation of T cells occurring in both organs.  More striking, the splenic
     T cells produced IL-10 in addition to IL-4, providing an environment that
     facilitated bystander deviation of responses to unrelated epitopes and
     promoted protection against experimental allergic encephalomyelitis
     involving diverse T cell specificities.  Thus, neonatal exposure to Ag can
     prime responses in various organs and sustain regulatory functions
     effective against diverse autoreactive T cells.


=> d his

     (FILE 'HOME' ENTERED AT 11:41:27 ON 19 SEP 2007)

     FILE 'MEDLINE, EMBASE, BIOSIS, SCISEARCH, CAPLUS' ENTERED AT 11:41:39 ON
     19 SEP 2007
L1       219919 S FUSION PROTEIN
L2          579 S L1 AND MYELIN BASIC  PROTEIN
L3           39 S L2 AND FC
L4           27 DUP REMOVE L3 (12 DUPLICATES REMOVED)
L5            9 S L4 AND PD<20010501
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L6         38982 S MYELIN BASIC PROTEIN
L7           858 S L6 AND FUSION
L8            44 S L7 AND FC
L9            32 DUP REMOVE L8 (12 DUPLICATES REMOVED)
L10           10 S L9 AND PD<20010501
L11           10 DUP REMOVE L10 (0 DUPLICATES REMOVED)
L12            4 S MYELIN BASIC PROTEIN CHIMERA
L13            1 DUP REMOVE L12 (3 DUPLICATES REMOVED)

=> s l6 and Ig fusion
L14           10 L6 AND IG FUSION

=> dup remove l14
PROCESSING COMPLETED FOR L14
L15            6 DUP REMOVE L14 (4 DUPLICATES REMOVED)

=> d l15 1-6 cbib abs

L15  ANSWER 1 OF 6  SCISEARCH  COPYRIGHT (c) 2007 The Thomson Corporation  on
     STN
2006:86182   The Genuine Article (R) Number: 001PK. Bone marrow transplantation
     combined with gene therapy to induce antigen-specific tolerance and
     ameliorate EAE.  Xu B Y; Haviernik P; Wolfraim L A; Bunting K D; Scott D W
     (Reprint). Univ Maryland, Dept Surg, Baltimore, MD 21201 USA (Reprint);
     Univ Maryland, Dept Microbiol & Immunol, Baltimore, MD 21201 USA; Case
     Western Reserve Univ, Div Hematol Oncol, Cleveland, OH 44106 USA;
     Tolergenics Inc, Rockville, MD 20850 USA; Ctr Stem Cell & Regenerat Med,
     Cleveland, OH 44106 USA. davscott@som.umaryland.edu. MOLECULAR THERAPY
     (JAN 2006) Vol. 13, No. 1, pp. 42-48. ISSN: 1525-0016. Publisher: ACADEMIC
     PRESS INC ELSEVIER SCIENCE, 525 B ST, STE 1900, SAN DIEGO, CA 92101-4495
     USA. Language: English.
     *ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS*
AB        Hematopoietic stem cell (HSC) transplantation is a potential therapy
     that can offer multiple sclerosis patients a radical, potentially curative
     treatment. Using experimental autoimmune encephalomyelitis (EAE) as a
     model, we previously reported that retrovirally transcluced B cells
     expressing myelin basic protein (MBP), MBP
     Ac1-11, or myelin oligodendrocyte glycoprotein p35-55 induced tolerance
     and reduced symptoms. Here, we extend our tolerance approach using bone
     marrow (BM) cells expressing full-length phospholipid protein (PLP) in a
     model for relapsing, remitting EAE. Using GFP expression as a marker, we
     found that up to 50% of cells were positive for transgene expression in
     peripheral blood after 900 rad irradiation and transcluced BM
     transplantation, and expression was stable in hematopoietic lineages for
     over 10 weeks. Upon challenge, T cell proliferation in response to PLP
     p139-151 was reduced and EAE was completely abolished in a pretreatment
     protocol. In addition, protection from EAE could be achieved with
     PLP-transduced BM cells given on day 12 after immunization, a potential
     therapeutic protocol. Finally, the protective effect of PLP-expressing BM
     could also be observed using a nonmyeloablative protocol, albeit with
     lower efficacy. Our results suggest that HSC may be useful to achieve
     long-lasting tolerance to protect mice from EAE and possibly to promote
     CNS repair in ongoing EAE.

L15  ANSWER 2 OF 6  CAPLUS  COPYRIGHT 2007 ACS on STN
2004:965060   Document No. 141:388749  Use of N-type calcium channel inhibitors
     in treating demyelinating diseases.  Smith, Terence; Tokuhara, Naoki;
     Niidome, Tetsuhiro (Eisai London Research Laboratories Limited, UK).  PCT
     Int. Appl. WO 2004096217 A1 20041111, 44 pp.  DESIGNATED STATES: W:  AE,
     AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR,
     CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU,
     ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA,
     MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU,
     SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC,
     VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK,
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ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2004-GB1691 20040421. PRIORITY: GB 2003-9509 20030425.

AB Inhibitors of N-type calcium channels are likely to be useful in treating demyelinating disorders and can be formulated as pharmaceutical compns.

L15 ANSWER 3 OF 6 MEDLINE on STN DUPLICATE 1

2002231870. PubMed ID: 11971030. Gene transfer of **Ig-fusion** proteins into B cells prevents and treats autoimmune diseases. Melo Marco E F; Qian Jiahua; El-Amine Moustapha; Agarwal Rajeev K; Soukhareva Nadejda; Kang Yubin; Scott David W. (Holland Laboratory, Department of Immunology, American Red Cross, Rockville, MD 20855, USA.) Journal of immunology (Baltimore, Md. : 1950), (2002 May 1) Vol. 168, No. 9, pp. 4788-95. Journal code: 2985117R. ISSN: 0022-1767. Pub. country: United States. Language: English.

AB Based on the tolerogenic properties of IgG carriers and B cell Ag presentation, we developed a retrovirally mediated gene expression approach for treatment of autoimmune conditions. In this study, we show that the IgG-Ag retroviral constructs, expressing **myelin basic protein** (MBP) or glutamic acid decarboxylase in B cells, can be used for the treatment of murine models for multiple sclerosis and diabetes. Transduction of syngeneic B cells with MBP-IgG leads to the amelioration of ongoing experimental allergic encephalomyelitis induced by the transfer of primed cells from PLxSJL F(1) mice with ongoing disease and could be effective even after symptoms appeared. This effect is specific and does not involve bystander suppression because treatment with MBP-IgG does not affect disease induced after immunization with proteolipid protein immunodominant peptide plus MBP. Interestingly, if donor B cells are derived from gld mice (Fas ligand-negative), then tolerance is not induced with a model Ag although there was no evidence for Fas ligand-mediated deletion of target T cells. In spontaneous diabetes in nonobese diabetic mice, we were able to stop the ongoing autoimmune process by treatment at 7-10 wk with glutamic acid decarboxylase-IgG retrovirally transduced B cells, or attenuate it with B cells transduced with an insulin B chain (B9-23) epitope IgG fusion protein. Furthermore, IgG fusion protein gene therapy can also protect primed recipients from Ag-induced anaphylactic shock, and thus does not cause immune deviation. These results demonstrate proof of principle for future efforts to develop this approach in a clinical setting.

L15 ANSWER 4 OF 6 CAPLUS COPYRIGHT 2007 ACS on STN

1998:126278 Document No. 128:191578 Soluble monovalent and multivalent MHC class II fusion proteins, and uses therefor. Wucherpfennig, Kai W.; Strominger, Jack L. (President and Fellows of Harvard College, USA; Wucherpfennig, Kai W.; Strominger, Jack L.). PCT Int. Appl. WO 9806749 A2 19980219, 77 pp. DESIGNATED STATES: W: AU, CA, JP, NZ, US; RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 1997-US14503 19970815. PRIORITY: US 1996-24077 19960816.

AB The present invention is directed to the design, production, and use of recombinant fusion proteins derived, in part, from the proteins of the human Major Histocompatibility Complex. The MHC II fusion proteins are useful for treating autoimmune diseases, e.g. multiple sclerosis or rheumatoid arthritis. The MHC class II includes HLA-DR1, HLA-DR2, HLA-DR4, HLA-DQ1, HLA-DQ2, and HLA-DQ8 α chain or β chain. Thus, DRA*0101 extracellular region-Fos leucine zipper domain and DRB1*1501 extracellular region-Jun leucine zipper domain fusion proteins, HLA-DR2 heterodimers (both DRα and DRβ), DR2-IgG fusion protein, and DR2-IgM fusion protein were prepared The prepared DR2-**Ig . fusion** proteins were used for selective depletion of T cells, or were complexed to toxins for inducing apoptosis of selective T cells.

L15 ANSWER 5 OF 6 SCISEARCH COPYRIGHT (c) 2007 The Thomson Corporation on STN

1995:414261 The Genuine Article (R) Number: RE574. ANTIGEN-PRESENTING T-CELLS

INDUCE THE DEVELOPMENT OF CYTOTOXIC CD4(+) T-CELLS .1. INVOLVEMENT OF THE CD80-CD28 ADHESION MOLECULES. MAURI D (Reprint); WYSSCORAY T; GALLATI H; PICHLER W J. INSELSPITAL BERN, INST IMMUNOL & ALLERGOL, CH-3010 BERN, SWITZERLAND; F HOFFMANN LA ROCHE & CO LTD, PHARMACEUT RES, NEW TECHNOL, CH-4002 BASEL, SWITZERLAND. JOURNAL OF IMMUNOLOGY (1 JUL 1995) Vol. 155, No. 1, pp. 118-127. ISSN: 0022-1767. Publisher: AMER ASSOC IMMUNOLOGISTS, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The development of cytotoxic CD4(+) T lymphocytes that can kill target cells in a MHC class II-restricted manner was evaluated by comparing different APCs. B-lymphoblasts (B-LCL) pulsed with the superantigen staphylococcus enterotoxin B or allogeneic B-lymphoblasts induce CD4(+) T cells without cytotoxic activity, In contrast, superantigen-pulsed, MHC class II+ T cell blasts or allogeneic T cell blasts preferentially induce the development of specific, MHC class Ii-restricted CD4(+) cytotoxic effector cells. CD4(+) T cell clones generated with T or B cell blasts as APCs (T- or B-APCs) differ in their cytolytic potential, but secrete a similar cytokine pattern. Our data implicate that activated T-APCs preferentially induce a cytotoxic, CD8(+) and CD4(+) T cell response. Because the density of CD80 expression is lower on activated T-APCs than on B-APCs, we studied the involvement of CD28 and CD80 adhesion molecules in the generation of CD4(+) CTLs. Partial blockade of the CD80 molecule with a CTLA4-**Ig fusion** protein and with specific anti-CD80 mAbs on B-APCs enhanced the generation of CD4(+) CTLs. Specific anti-CD86 mAbs, on the contrary, had no effect on the generation of CD4(+) CTLs. In contrast, stimulation of CD28, the CD80 counter-receptor, with a cross-linked B7-**Ig fusion** protein or with an anti-CD28 mAb, inhibited the generation of CD4(+) CTLs. Thus, a reduced interaction between CD80 and CD28 may be relevant for the induction of CD4(+) CTLs. This shows a new and not yet described function of these adhesion molecules. This induction of a cytotoxic immune response by T cells as APCs may be relevant for the anticlonotypic regulation of T cells and for the depletion of CD4(+) T cells in HIV infection.

L15 ANSWER 6 OF 6 SCISEARCH COPYRIGHT (c) 2007 The Thomson Corporation on STN

1995:24928 The Genuine Article (R) Number: PZ242. B7/BB-1 ANTIGEN EXPRESSION ON ADULT HUMAN MICROGLIA STUDIED IN-VITRO AND IN-SITU. WILLIAMS K (Reprint); ULVESTAD E; ANTEL J P. MCGILL UNIV, MONTREAL NEUROL INST, DEPT NEUROL & NEUROSURG, NEUROIMMUNOL UNIT, MONTREAL, PQ, CANADA; UNIV BERGEN, GADE INST, DEPT MICROBIOL & IMMUNOL, BERGEN, NORWAY. EUROPEAN JOURNAL OF IMMUNOLOGY (DEC 1994) Vol. 24, No. 12, pp. 3031-3037. ISSN: 0014-2980. Publisher: VCH PUBLISHERS INC, 303 NW 12TH AVE, DEERFIELD BEACH, FL 33442-1788. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB In this study, we have examined the expression and function of B7/BB-1 on individual glial cells, by utilizing surgically resected adult human central nervous system (CNS) tissues, tissues derived from fetal human CNS, and pathology material from cases of multiple sclerosis (MS). Immunofluorescence analysis using enriched adult human derived cultures of microglia and oligodendrocytes, and mixed microglia/astrocyte cultures, demonstrated that B7/BB-1 was expressed on microglia. Adult human-derived oligodendrocytes and astrocytes, and human fetal astrocytes were B7/BB-1 negative under all culture conditions. Flow cytometry studies demonstrated a low basal level of B7/BB-1 expression on microglia that was up-regulated following incubation with interferon-gamma (IFN-gamma). Go-culture of purified fresh allogeneic CD4(+) T cells with microglia for 24 h resulted in clustering of T cells around microglia and microglial B7/BB-1 expression. Preincubation of microglia with an anti BB-1 monoclonal antibody (mAb) prior to microglia: CD4(+) T cell co-cultures resulted in partial inhibition of the ability of microglia both to present recall antigen to autologous CD4(+) T cells and to present antigen to allogeneic CD4(+) T cells in primary mixed lymphocyte reaction (1 degrees MLR). The CTLA-4 **Ig fusion** protein inhibited the

ability of microglia to present antigen in both antigen presentation assays to an even greater extent than did the anti BB-1 mAb. The BB-1 antibody also inhibited the ability of microglia to stimulate previously activated T cells in a secondary 2 degrees MLR. In sections of multiple sclerosis brain, B7/BB-1 expression was observed on activated microglia in select parenchymal lesions, and on perivascular cells and infiltrating monocytes. B7/BB-1 immunoreactivity was not found in normal appearing white matter from MS brain or from non-inflammatory brain specimens. Our results indicate that the B7/BB-1 molecule plays a functional role in the capacity of microglia to serve as CNS antigen-presenting cells that can both initiate and perpetuate CD4(+) T cell activation.

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L18 2 DUP REMOVE L17 (4 DUPLICATES REMOVED)

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L18 ANSWER 1 OF 2 MEDLINE on STN DUPLICATE 1
96193897. PubMed ID: 8613536. In vivo neutralization of eosinophil-derived major basic protein inhibits antigen-induced bronchial hyperreactivity in sensitized guinea pigs. Lefort J; Nahori M A; Ruffie C; Vargaftig B B; Pretolani M. (Unite de Pharmacologie Cellulaire, Institut National de la Sante et de la Recherche Medicale, Paris, France.) The Journal of clinical investigation, (1996 Feb 15) Vol. 97, No. 4, pp. 1117-21. Journal code: 7802877. ISSN: 0021-9738. Pub. country: United States. Language: English.

AB This study examines the effect of purified rabbit antiguinea pig eosinophil-derived major basic protein (**MBP**) **Ig** on antigen-induced bronchial hyperreactivity to inhaled acetylcholine in aerosol-sensitized guinea pigs. Ovalbumin inhalation by sensitized guinea pigs induced a rise in the numbers of eosinophils and in the levels of MBP in the bronchoalveolar lavage fluid, which peaked at 24 h and resolved at 72 h. Antigen-challenged animals exhibited bronchial hyperreactivity to inhale acetylcholine at 72 h, but not at 6 or 24 h. The intranasal administration of 200 microliter of purified rabbit anti-guinea pig **MBP Ig**, at 2.5 mg/ml, but not of the control preimmune rabbit Ig, 1 h before and 5 h after ovalbumin inhalation suppressed bronchial hyperreactivity to acetylcholine at 72 h without affecting the number of eosinophils accumulating in the bronchoalveolar lavage fluid. These findings indicate that antigen challenge in sensitized guinea pigs is followed by early eosinophil infiltration and activation within the airways and by late bronchial hyperreactivity. Neutralization of endogenously secreted MBP by a specific antiserum prevented antigen-induced bronchial hyperreactivity, suggesting that eosinophil degranulation plays an important role in the alterations of bronchopulmonary function in the guinea pig.

L18 ANSWER 2 OF 2 EMBASE
92051372 EMBASE Document No.: 1992051372. Characterization of rat liver mannan-binding protein gene. Wada M.; Itoh N.; Ohta M.; Kawaski T.. Dep. of Biological Chemistry, Faculty of Pharmaceut. Scien., Kyoto University, Sakyo-ku,Kyoto, Kyoto 606, Japan. Journal of Biochemistry Vol. 111, No. 1, pp. 66-73 1992.
ISSN: 0021-924X. CODEN: JOBIAO
Pub. Country: Japan. Language: English. Summary Language: English.
Entered STN: 920320. Last Updated on STN: 920320

AB We previously found that rat liver mannan-binding protein (L-**MBP**) **ig** encoded by two species of mRNA of 1.4 and 3.5 kb long. In this study, the structure of the gene encoding rat L-MBP was determined from the sequences of isolated genomic DNA clones and PCR amplified DNA fragments. Rat L-MBP is encoded by at least three species of mRNA, the differences among which are generated by an alternative splicing at the 5'-nontranslated region and an alternative utilization of polyadenylation sites. The rat L-MBP gene consists of six exons separated by five introns. The coding region of rat L-MBP mRNA is encoded by four exons (Exons III-VI), the 5'-noncoding region by Exons I and II, and the 3'-noncoding region by Exon VI. The exon-intron boundaries of L-MBP are completely identical to those of rat serum and human MBP, suggesting that all three MBPs are derived from a common ancestral gene.

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=> s l19 and fusion
L20 64 L19 AND FUSION

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L21 2 L20 AND MYELIN BASIC PROTEIN

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=> d l22 1-2 cbib abs

L22 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2007 ACS on STN
2003:260853 Document No. 138:285999 Chimeric proteins comprising ITIM motif, antigen and FcεR binding peptide for treating immune diseases. **Saxon, Andrew** (USA). U.S. Pat. Appl. Publ. US 2003064063 A1 20030403, 51 pp., Cont.-in-part of U.S. Ser. No. 847,208. (English). CODEN: USXXCO. APPLICATION: US 2001-439 20011024. PRIORITY: US 2001-847208 20010501.

AB The invention concerns bifunctional **fusion** mols., and novel, safer and more efficacious methods for the treatment of immune disorders resulting from excessive or unwanted immune responses. The invention provides methods for the suppression of type I hypersensitive (i.e., IgE-mediated) allergic conditions, methods for the prevention of anaphylactic responses that occur as a result of traditional peptide immunotherapies for allergic and autoimmune disorders, and provides novel methods for the treatment of autoimmune conditions, where the methods have reduced risk of triggering an anaphylactic response. The invention provides novel therapeutic approaches for the treatment of allergic responses, including the prevention of anaphylactic response that can occur from environmental allergen exposure. The invention also provides methods for the treatment of autoimmune disorders such as multiple sclerosis, autoimmune type I diabetes mellitus, and rheumatoid arthritis. The invention also provides methods for preventing anaphylactic response during traditional antigen therapies.

L22 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2007 ACS on STN
2002:849789 Document No. 137:368556 Chimeric proteins comprising IgG inhibitory receptor-binding epitope and IgE receptor-binding epitope for treating allergies and other immune diseases. **Saxon, Andrew**; Zhang, Ke; Zhu, Daocheng (Regents of the University of California, USA). PCT Int. Appl. WO 2002088317 A2 20021107, 116 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, CZ, DE, DE, DK, DK, DM, DZ, EC, EE, EE, ES, FI, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US,

UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2002-US13527 20020501. PRIORITY: US 2001-847208 20010501; US 2001-439 20011024.

AB The invention concerns bifunctional **fusion** mols., and novel, safer and more efficacious methods for the treatment of immune disorders resulting from excessive or unwanted immune responses. The invention provides methods for the suppression of type I hypersensitive (i.e., IgE-mediated) allergic conditions, methods for the prevention of anaphylactic responses that occur as a result of traditional peptide immunotherapies for allergic and autoimmune disorders, and provides novel methods for the treatment of autoimmune conditions, where the methods have reduced risk of triggering an anaphylactic response. The invention provides novel therapeutic approaches for the treatment of allergic responses, including the prevention of anaphylactic response that can occur from environmental allergen exposure. The invention also provides methods for the treatment of autoimmune disorders such as multiple sclerosis, autoimmune type I diabetes mellitus, and rheumatoid arthritis. The invention also provides methods for preventing anaphylactic response during traditional antigen therapies.

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